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13. ABSTRACT *(Maximum 200 words)*

The objective of the research program was to investigate nonlinear optical phenomena and optical amplification and lasing in highly scattering active and non-active random media. The aim of research was to develop a deeper fundamental understanding of light propagation in active random media for future generation of optical display, imaging techniques and laser devices. Two photon excited fluorescence and second harmonic generation tomographic imaging of biomedical tissues were demonstrated. Lasing and optical amplification from dyed active turbid media and biological tissues were explored. A feedback mechanism from scattering walls was proposed to describe lasing characteristics in random media. We have published 12 papers and submitted two patent applications.

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Abstract

The objective of the research program was to investigate nonlinear optical phenomena and optical amplification and lasing in highly scattering active and non-active random media. The aim of research was to develop a deeper fundamental understanding of light propagation in active random media for future generation of optical display, imaging techniques and laser devices. Two photon excited fluorescence and second harmonic generation tomographic imaging of biomedical tissues were demonstrated. Lasing and optical amplification from dyed active turbid media and biological tissues were explored. A feedback mechanism from scattering walls was proposed to describe lasing characteristics in random media.

1. Objective:

The objective of this research program is to investigate nonlinear optical phenomena, optical amplification and lasing in highly scattering, active and non-active disordered media.

2. Summary of Research Results:

During the grant period, we have made significant progress in understanding the nonlinear optical processes, lasing and optical amplification, and nonlinear optical imaging in random media.

The following highlights our scientific accomplishments achieved during three and half years.

2a. Nonlinear Optical Processes and imaging in turbid media

Optical imaging is emerging as a novel and noninvasive in situ method for characterization and visualization of structures of biomedical tissues. Imaging techniques based on nonlinear optical (NLO) processes offer certain advantages in various medical imaging applications. Nonlinear optical techniques provide a higher spatial resolution that results from higher-power dependence of NLO signal (e.g. quadratic for a two-photon process and cubic for a three photon process) on the excitation intensity. NLO signal predominantly originates from around the focal point while linear optical signal arises from the entire illuminated region. NLO processes in random media are new. Optical sectioning is achieved in NLO techniques without using a confocal pinhole to yield the structural details inside biological tissues. Near-infrared light in the therapeutic window of 700-1300nm was used for a two-photon (TP) process, whereas a one-photon process would require the use of 350-650 nm light for exciting the same transitions. Since NIR light is much less scattered and absorbed by tissue constituents than the visible light, deeper penetration into the tissue may be attained. Transitions are not accessible to a one-photon (P) process may be excited by a NLO process, such as TP absorption. The dependence of NLO signal on coherence, polarization, wavelength and intensity of exciting radiation as well as on the site symmetry of the sample provides additional information to better characterize tissue over linear approaches.

We studied harmonic generation (second harmonics and third harmonic generations) and two photon excited fluorescence generated in biological tissues by ultrashort laser pulses. NLO signal intensity and spectroscopic signature are found to correlate with tissues type. [see publication #7, and #8] This finding provided fundamentals for non-invasive imaging of tissues using NLO signals. Different components of tissues can be highlighted by detecting different NLO signal.

We imaged tryptophan distribution in high scattering native biological tissues by selectively excite (625 nm pump) and detect fluorescence from tryptophan molecules (320 to 260 nm).[see publication #5 and #4] 100 fs light pulses from a colliding-pulse mode locked dye laser were used. A two-dimensional map of the tryptophan distribution in a chicken-tissue sample was obtained by scanning the laser beam over the tissue surface and accumulating the fluorescence signal point-by-point with a photo multiplier tube and a lock-in amplifier system. Images of a tissue at an axial position up to 250μm from the surface were recorded with a lateral resolution of ~ 10 μm.

Second harmonic (SHG) signal was used to image subsurface structure of chicken tissues. Different layer structures are highlight in SHG images.[see publication #6 and #4] SHG imaging was used to evaluate the subsurface tumor progression in control, dysplasia and cancerous of DMBA treated hamster cheek pouch mucosa tissues using femtosecond laser technology. Two dimension images of hamster cheek pouch mucosa were obtained by scanning the second harmonic signal at various lateral and axial positions. The spatial mapping of the second harmonic signal showed depth differentiation between normal, dysplasia, and a more advance cancerous states.[see publication #2]

Scattering is a significant factor for imaging biological tissues using NLO technique. We have studied the spatial distribution of TPF beneath the surface of random scattering media. It is found that scatter in the medium affects the NLO signal. When scattering is strong, NLO generated near the sample surface is found to be at the same level as the NLO signal produced at focal region. Scattering degrades the spatial resolution of the NLO signal, which limits the imaging depth to a few scattering lengths. A theoretical model was developed to qualitatively explain the experimental observations. [see publication #1 and #3]

NLO imaging technique is wavelength selective, morphology dependent, and molecule specific. This method offers potential for a less invasive method by giving the analysis of certain molecules in tissue structures. This nonlinear optical method offers a novel and new in situ histological tool for the medical community. The NLO imaging technique can also be applied in other field like semiconductor chip inspection, and non-destructive corrosion detection.

2b. Amplification and laser action in active random media and biological tissues.

Scattering in active medium provides a feedback mechanism for stimulated emissions. Compared to nonscattering active media, the lasing threshold is decreased when scattering strength of the media is increased.

Laser action of Sulforhodamine 640 and Rhodamine 640 perchlorate in scattering media consisting of different types (R100, R900, and R960 for TiO_2) and concentrations ($5.0x10^9$ to $1.0x10^{12}$ cm^{-3}) of titanium dioxide particles in methanol was investigated in the spectral and temporal measurements pumped by a 3 ns at 530 nm laser pulse. The lasing threshold energy with particles is dependent on the concentration of both laser dye and density of coated and uncoated particles. The threshold was found to be reduced by over one to two orders of magnitude, The bandwidth of emission and the temporal width of the emission pulse were dramatically narrowed. The bandwidth of emission spectra depended on the particle densities; the optimum density of particle was found to be about $5.0x10^{10}$ cm^{-3}.

Emission characteristics from Rhodamine 640 perchlorate samples were found to have two lasing bands. The dominating lasing band was found to switch from 650 nm to 620 nm band when the particle density is above 10^{11} cm^{-3}.[see publication #10]

We explored the mechanism for lasing by comparing ultrafast emission measurements on a time scale comparable with the residence time of the pump photons in the medium and much short than the excited-state lifetime to a Monto Carlo simulation of photon migration and level occupation. The temporal profiles of the emission from titania particle suspensions in Rhodamine 640 perchlorate dye solution excited by 10-ps pulses of 527-nm radiation were measured over a wide range of particle and dye

concentrations and laser powers. The dynamics of stimulated emission from random media is modeled by a random walk of photons within the colloid and rate equations for molecular excitations. The pulse width and dependence of the threshold for laser action on dye and scatter concentration are computed by a Monte Carlo simulation of the model and are found to be in qualitative agreement with experimental measurements. The temporal pulse profile of emission is found to be a more sensitive indication of the onset of stimulated emission than the changes in spectral profiles.[see publication #11]

A systematic study of laser action in discrete-disordered condensed media and continuous disordered animal tissues in optically active dye host was undertaken using temporal and spectral measurements to support a "feedback mechanism" from the surrounding scattering walls of the host medium. Significant narrowing of both the spectral and temporal profiles of emission radiation from optically pumped dyes in discrete and continuously disordered media such as dilute colloidal dye solutions and densely-packed form of sandy powders and animal tissue treated with Rhodamine 640 dye solution was observed. The narrowing of the spectral and temporal responses is attributed to laser action arising from the feedback of the emission radiation from the surrounding scattering walls into the photoexcited dye regions of the animal and sandy colloidal disordered media. [see publication #12]

The scientific results obtained from this research deepen our understanding of light propagation in active random media. These finding can be important to develop new generation of low threshold or threshold less lasers and high efficient optical LED displays.

3. Personnel:

Principle Investigator: Professor R. R. Alfano,

Researchers: Ms. C.-H. Liu (research associate)
Dr. Feng Liu (research associate)
Dr. J. Ying (research associate)
Mr. M. Siddique (PhD graduate student)
Ms. Yici Guo (Ph. D. Graduate student, graduated 1998)
Ms. W.L. Sha (Ph. D graduate student)

Educational Achievement:

Ms. Yici Guo completed her Ph. D. thesis work under the support of this grant. She graduated in September, 1998. She is currently employed by AT&T.

Ms. W. L. Sha resigned during the middle of this grant period. She is currently employed by IBM.

4. Publications, Presentations, and Patent:

Publications:

1. J. Ying, F. Liu, and R. R. Alfano, "Effect of scattering on nonlinear optical signal scanning microscopy imaging of highly scattering media," Appl. Opt. Vol. 39, page 509-514(2000)

2. Yici Guo, Howard E. Savage, Feng Liu, Stimson P. Schantz MD, P. P. Ho, and R. R. Alfano, "Subsurface Tumor Progression Investigated by Noninvasive Optical Second Harmonic Tomography," Proc. Natl. Acad. Sci. USA, Vol 95, page 10854-10856 (1999).
3. Jinpin Ying, Feng Liu, and R. R. Alfano, "Spatial distribution of two-photon excited fluorescence in scattering media," Appl. Opt. Vol. 38, 224-229(1999).
4. Yici Guo, F. Liu, Q.Z. Wang, N. Zhadin, P.P. Ho, H. Savage, D. Harris, P. Sacks, S. Schantz and R.R. Alfano, "Second harmonic and two photon fluorescence histology of tissues", SPIE vol. 3250, p210(1998).
5. Yici Guo, P.P.Ho, F. Liu, Q.Z. Wang, R.R. Alfano, "Noninvasive two-photon-excitation imaging of tryptophan distribution in highly scattering biological tissues", Optics Communications, 154, p.383(1998).
6. Yici Guo, P.P. Ho, H. Savage, D. Harris, P. Sacks, S. Schantz, F. Liu, N. Zhadin, and R.R. Alfano, "Second-harmonic tomography of tissues", Optics Letters, Vol. 22, No. 17, P1323(1997).
7. Yici Guo, Q. Z. Wang, N. Zhadin, Feng Liu, S. Demos, D. Calistru, A. Tirksliunas, A. Katz, Y. Budansky, P. P. Ho, and R. R. Alfano, "Two photon excitation of fluorescence from chicken tissue," Appl. Opt. **36**, 968-970(1997)
8. Yici Guo, P. P. Ho, A. Tirksliunas, Feng Liu, and R. R. Alfano, "Optical harmonic generation from animal tissues by the use of picosecond and femtosecond laser pulses," Appl. Opt. **35**, 6810-6813(1996)
9. Yici Guo, F. Liu, Q.Z. Wang, H.E. Savage, N. Zhadin, P.P. Ho, S. Schantz, and R.R. Alfano, "Nonlinear Optical Histological Spectroscopy and Imaging of Biological Tissues", Advances Optical Imaging and Photon Migration, OSA March 1998.
10. W.L. Sha, C.-H. Liu, F. Liu, and R.R. Alfano, "Competition between two lasing modes of Sulforhodamine 640 in highly scattering media", Optics Letters Vol.21,No.16, 1277 (1996).
11. M. Siddique and R.R. Alfano, G.A. Berger, M.Kempe, and A.Z. Genack, "Time-resolved studies of stimulated emission from colloidal dye solutions", Optics Letters, Vol. 21, No.7, 450 (1996).
12. M. Siddique, Q.Z. Wang, and R.R. Alfano, "Laser action in condensed disordered media of active dye-stained animal tissues and sandy colloidal scattering walls", Journal of Biomedical Optical, Vol.1, No.4, pp1-6 (1996).

Conference Presentations:

1. Yici Guo, H.E. Savage, F. Liu, S.P. Schantz, P.P. Ho, R.R. Alfano, "Optical second-harmonic tomography of subsurface tumor evaluation", OSA Annual Meeting, Baltimore, Maryland, WM7, Oct. 1998.
2. F. Liu, Y. Guo, R.R. Alfano, P.P. Ho, H.E. Savage and S.P. Schantz, Fifth Research Workshop on the Biology Prevention and treatmented of Head and Neck Cancer, (Viginia, Aug., 1998) HN77.
3. F. Liu, "Subsurface structure mapping of biological tissues using second-harmonic and two-photon fluorescence by ultrashort laser pulses", WM1 invited paper, OSA Annual Meeting, Baltimore, Maryland, WM1, Oct. 1998.

4. J. Ying, F. Liu, R.R. Alfano, "Spatial distribution of two-photon excited fluorescence in scattering media", WM4, OSA Annual Meeting, Baltimore, Maryland, Oct. 1998.
5. Y. Guo, F. Liu, N.N. Zhadin, P. Ho, H.E. Savage, D. Harris, P.G. Sacks, S.P. Schantz, R.R. Alfano, "Second harmonic and two-photon fluorescence nonlinear optical histology of tissues", 3250-33, BIOS'98 international Biomedical Optics Symposium", 1998.
6. C.-H. Liu, F. Liu, W.L. Sha, and R.R. Alfano, "Competition between two lasing modes of Sulforhodamine 640 in highly scattering media", CTHG3, CLEO'96 Anaheim, California, June 2-7, 1996.

Patent Disclosure:

1. Title: "Light Amplification in Dye-Stained Biological Tissues",
   Inventor: R.R. Alfano and M. Siddique.
   Date: June, 1997.
2. Title: "Non-linear optical tomography histology of highly scattering turbid and biomedical media",
   Inventor: R.R. Alfano Y. Guo, F. Liu, and P. P. Ho
   Date: April, 1997